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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PERLINGER, SARAH E	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 07/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,104	BECKER ET AL.	
	Examiner	Art Unit	
	Sarah E. Perlinger	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,10,11,13,14,16,17,20-36 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *2-3, 9,12,15, 18-19,37-61 and 63-83* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-83 are pending.

2. ***Election/Restrictions***

Applicant's election with traverse of Group I in the reply filed on April 17, 2006 is acknowledged. The traversal is on the ground that the compounds of the different groups are not so distinct as to place an undue burden on the examiner. This is not found persuasive because the compounds of groups I-VI are independent and distinct compounds because no common core among the various groups can be identified. Lacking common core, the search for each different core structure is not coextensive as evidenced by the diversity of classification. In the instant case, the compounds of groups I-VI are classified separately as illustrated in the restriction requirement sent March 23, 2006 and it would be extremely burdensome to search such diverse core structures. Each independent core structure is classified separately and requires a separate search in the electronic databases. The compounds of groups I-VI also differ in elements, bonding arrangement and chemical property to such an extent as to not be in a general class of compounds recognized in the chemical art.

Furthermore, the restriction requirement sent on March 23, 2006, required an election of a single disclosed species. In the reply filed April 17, 2006, applicants elected claim 32. In a subsequent telephonic communication on June 22, 2006, applicants elected the species of formula (32-1) wherein A1 is hydroxyl, E1 is pyridyl and E2 is phenyl. Claims 9, 12, 15, 18-19, 37-61, 63-83 are drawn to non-elected inventions. Based on the election of species (32-1), claims 1, 4-8, 10-11, 13-14, 16-17, 20-36 and 62 reading on A1 is hydroxyl, E1 is optionally substituted pyridyl, E2 is optionally substituted phenyl and E3 and E4 as defined in claim 1 will be examined on the merits.

Should applicant traverse on the ground that the groups are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the groups to be obvious

variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention. In the instant case, there would have been no patentability of all the claims over any of the claims because Barta et al., US 6,541,489 anticipates claims 1, 4-8, 10-11, 13-14, 16-17, 20-40, 46, 49-54, 62, 76 (see US 6,541,489, column 402, line 13).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The requirement is still deemed proper and is therefore made FINAL.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 56-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are indefinite where a method for treating a condition "associated with" pathologically excessive matrix metalloprotease, TNF-α convertase, or aggrecanase activity is claimed. It is unclear how a condition is "associated with" pathologically excessive matrix metalloprotease, TNF-α convertase, or aggrecanase activity or what conditions the instant claims include or exclude. The scope of claims 56-58 cannot be ascertained due to the vague terminology used.

4. Claims 56-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are indefinite where a method for treating a condition associated with "pathologically

excessive" matrix metalloprotease, TNF-a convertase, or aggrecanase activity is claimed. The phrase, "pathologically excessive" is subjective. What is "pathologically excessive" for one enzyme in one physiological condition may be detrimental for another enzyme. Furthermore, what is "pathologically excessive" for one mammal may not be "pathologically excessive" for another mammal and therefore it is impossible to determine what conditions the instant claimed method would apply to. The scope of claims 56-58 cannot be ascertained due to the subjective terminology used.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56, 58-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a method of treating such an enormous variety of conditions associated with pathologically excessive matrix metalloprotease, TNF-α convertase, or aggrecanase activity in a mammal, such as tissue destruction, a fibrotic disease, matrix weakening, defective injury repair, a cardiovascular disease, a pulmonary disease, a kidney disease, a liver disease, an ophthalmologic disease, and a central nervous system disease. A survey of the specification revealed description of methods for carrying out an *in vivo* angiogenesis assay, an *in* vitro tumor necrosis factor assay, and an *in vitro* aggrecanase inhibition assay. No data was found that illustrated any of the instant claimed compounds displaying angiogenic inhibitory activity, TNF-α inhibitory activity, or aggrecanase inhibitory activity. Furthermore, no support was found for any of the compounds being able to treat any pathology or symptom, nor was any pathology or

symptom inexorably linked to the inhibition of angiogenesis, TNF-α, or aggrecanase at any specific dosage (see Specification, pages 223-230).

6. Claims 56, 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a method for treating a condition associated with pathologically excessive matrix metalloprotease (MMP). A survey of the specification revealed description of selected species' inhibition of MMP-1, MMP-2, MMP-9, MMP-13 and MMP-14. No data was found that illustrated any of the instant claimed compounds displaying inhibition of all MMP types including MMP-3, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12. Furthermore, the data found in the specification suggested the instant claimed compounds displayed little or no inhibition activity toward MMP-1 and MMP-14 (see Specification, pages 211-222).

7. Claims 56, 58-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

Nature of Invention

Claims 56-61 are drawn to a method for treating such a diversity of disorders for example as tissue destruction, a fibrotic disease, matrix weakening, defective injury repair, a cardiovascular disease, a

pulmonary disease, a kidney disease, a liver disease, an ophthalmologic disease, and a central nervous system disease in a mammal comprising administering a therapeutically effective amount of a compound of claim 1. No nexus exists among the diversity of such disorders which have multiple and unrelated etiology.

The State of the art and Predictability

The current state of the medical art is disease and symptom-oriented, for example, treating diabetes mellitus ordinarily has the connotation of treating impaired glucose tolerance, treating hypertension ordinarily has the connotation of lowering blood pressure. Furthermore, treating Alzheimer's disease or treating atherosclerosis, encompassed by the scope of the claims, included treating multi-factorial diseases. Such treatments involved complex processes including the interaction of multiple factors such as injury, response, etc.

The state of the art in multi-functional disease treatment is extremely controversial and the complete etiology of such disease (i.e. atherosclerosis) remains unknown. "Our full understanding of atherosclerosis and our ability to prevent its sequellae are incomplete" (see summary of Heinonen, *Current Atherosclerosis Reports,* 2002, 4(1), 65-70). "Experimental studies have shown the regression of atherosclerosis in animals given a cholesterol-rich diet and then given a normal diet or hypolipidemic therapy. Despite favourable results of clinical trials of primary prevention modifying the lipid profile, the concept of atherosclerosis regression in man remains very controversial" (see summary of Thomas et al., *Archives des Maladies du Coeur et des Vaisseaux*, 1992, 85, III, 47-57).

The same analogy can be found in treating a neurological disorder such as neurodegenerative disease, including those such as Alzheimer's disease, Parkinson's disease, etc. has been well recognized in the art to be literally untreatable (see CA 126:324757). In addition, in so far as neuropathies are concerned, it is well recognized that many neuropathies have different etiology and treatment of such

conditions is highly specific. In absence of specific description of enablement, one skilled in the art is unable to operate such process (see CA 127:174580).

Furthermore, for the CNS related neurological disorders, it is a well-known fact that any compound having CNS efficacy must cross the blood brain barrier. No description for the instant claimed compounds having the ability to cross the blood-brain barrier has been provided.

Finally, the failure of many hydroxamate compounds for clinical use as MMP inhibitors is well documented in the art. The hydroxamate compounds, though having *in vitro* MMP inhibiting activity, have had shortcomings in clinical use such as being rapidly metabolized, showing poor selectivity profiles amongst the different MMP's, poor bioavailability, and toxic side effects (see for example, Breuer et al., *Expert Opin. Ther. Patents,* 2005, 15(3), 253-269, especially page 254).

The amount of guidance and working examples

The specification is limited to a description of methods for carrying out an *in vivo* angiogenesis assay, an *in vitro* tumor necrosis factor assay, and an *in vitro* aggrecanase inhibition assay. No data was provided to illustrate that any of the instant claimed compounds actually displayed angiogenic inhibitory activity, TNF-α inhibitory activity, or aggrecanase inhibitory activity. Furthermore, no support was found that any of the compounds are able treat any pathology or symptom, nor was any pathology or symptom inexorably linked to inhibition of angiogenesis, TNF-α, or aggrecanase at any specific dosage.

In view of the extreme diversity in structure of compounds of claim 1, and absent of any correlation between which compound was effective with respect to which disorder/enzyme, one having ordinary skill in the art was offered no guidance to pick and choose for the individual compound for a method of treatment. In view of the state of the art in hydroxamate compounds' lack of clinical success in inhibiting MMPs, mere *in vivo* and *in vitro* angiogenic, TNF-α, and aggrecanase assays do not provide description or enablement for treatment of disease associated with multiple enzyme involvement in any

mammal for which dosage, site of administration and the length of time for which a compound is administered, must be made known to one having ordinary skill in the art to practice such method. Section 112 requires the application itself to inform, not for others to fine out by themselves. Ex parte Aggarwal 23 USPQ 2nd 1481. In re Gardner 166 USPQ 138.

No data or examples were provided for the compound as claimed in claim 1, illustrating which compound was effective with respect to specific neurological disorders in order to guide one having ordinary skill in the art to pick and choose for the individual method of treatment. In view of the absolute requirement for a compound to cross the blood-brain barrier in order for it to have efficacy in the CNS, no description or enablement can be found that the claimed compound would have any practical CNS method of use.

The specification provides none of the composition or dosage preparation or guidelines for a CNS route of administration, i.e. no guidance was provided in the specification for intracranial administration (see Specification, pages 79-85).

One etiological mechanism that can treat such a diversity of diseases as tissue destruction, a fibrotic disease, matrix weakening, defective injury repair, a cardiovascular disease, a pulmonary disease, a kidney disease, a liver disease, an ophthalmologic disease, and a central nervous system disease in a mammal has not been found in the specification. Also, no nexus between inhibiting angiogenesis, TNF-α, or aggrecanase to the treatment of such a diversity of conditions in a mammal has been seen in the specification.

8. ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

> such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-8, 10-55, 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barta et al. (see WO 99/25687, examples illustrated at pages 542-545, 551, 557-558, 560-561, pages 735-738, claim 1, page 764, claim 28, pages 771-778, claim 52 and pages 788-789, claim 69 or WO 00/50396, pages 541-550, compounds 213-223, 225-226, 228, 230-232, pages 743-746, claim 1, pages 779-787, claim 52 and pages 796-797, claim 69).

Determination of the scope and content of the prior art (MPEP§ 2141.01)

Barta et al. taught specific compounds as illustrated on pages 542-545, 551, 557-558, 560-561, wherein A1 is hydroxyl, E1 is phenyl, E2 is phenyl and E3 and E4 are within the scope of the instant claims (see WO 99/25687).

Barta et al. also taught specific compounds as illustrated on pages 552-559 wherein A1 is hydroxyl, E1 is phenyl, E2 is phenyl and E3 and E4 are within the scope of the instant claims (see WO 00/50396).

Both Barta et al. references generically disclosed structurally similar compounds against the base claims as delineated (see WO 99/25687, pages 735-738, claim 1, page 764, claim 28 and pages 771-778, claim 52 and pages 788-789, claim 69 or WO 00/50396, pages 743-746, claim 1, pages 779-787, claim 52 and pages 796-797, claim 69). Furthermore, both Barta et al. references taught MMP active compounds with a Markush group fully encompassing the instant claims. Further, E1 is aryl or heteroaryl including phenyl and pyridyl.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The only difference between the instant claimed compound and the reference compound is that instead of E1 being a phenyl, E1 of the instant claimed species is a pyridyl. Barta et al. however, generically disclosed heteroaryl and aryl groups as being interchangeable at the E1 position and disclosed a structurally similar species wherein the Z-containing ring is a tetrahydropyran (see for example, WO

99/25687, pages 542-545, 551, 557-558, 560-561, 750 or WO 00/50396, pages 552-559, 758). It is also well known in the art that the bonding in pyridyl and phenyl rings is analogous and the size of the two ring types is very similar (see Lide, CRC Handbook of Chemistry and Physics, page 9-5).

Finding of prima facie obviousness-rationale and motivation (MPEP § 2142-2143)

One having ordinary skill in the art in possession of Barta et al. WO 99/25687 or WO 00/50396 would be in possession of the instant claims **because** the generic disclosure fully encompassed species of the instant claims (see WO 99/25687, pages 735-738, claim 1, page 764, claim 28, pages 771-778, claim 52 and pages 788-789, claim 69 or WO 00/50396, pages 743-746, claim 1, pages 779-787, claim 52 and pages 796-797, claim 69). Also, Barta et al. illustrated several structurally similar species wherein E1-E2 is a biphenyl group (see WO 99/25687, examples illustrated at pages 542-545, 551, 557-558, 560-561 or WO 00/50396, pages 541-550, compounds 213-223, 225-226, 228, 230-232). One having ordinary skill in the art would be motivated to choose pyridine for the E1 position **because** Barta et al. illustrated that the E1-E4 side chain is size sensitive (see WO 99/25687, page 764, claim 28 or WO 00/50396, page 772, claim 28). Therefore, replacement of the side chain by picking and choosing the analogous size moiety (i.e. phenyl) within the generic alternatives has been as a whole, clearly guided by the prior art. Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention, to prepare any of the species of the genus taught by the reference, including those of the claims, because an ordinary artisan would have the reasonable expectation that all of the species of the genus, especially those having the optimal size as set forth by Barta et al. WO 99/25687 or WO 00/50396, would have similar properties and, thus, the same use as the genus as a whole (see *In re* Lemin 141 USPQ 814).

9. Claims 50-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barta et al. WO 00/69821 (see WO 00/69821, pages 558-566, claim 1, and pages 585-594, claim 25) in view of Barta et al. WO 99/25687 (see, WO 99/25687, pages 735-738, claim 1 and page 764, claim 28).

Determination of the scope and content of the prior art (MPEP§ 2141.01)

Both Barta et al. references generically disclosed structurally similar compounds having utility as inhibitors of matrix metalloproteinase against the base claims as delineated.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The only difference between the instant claimed compound and the reference compound is that instead of E1 being an aryl group, E1 of the instant claimed compound is a heteroaryl group. Barta et al. however, disclosed a structurally similar compound wherein E1 is optionally a heteroaryl or aryl group (see WO 99/25687, pages 542-543, examples 219-221, page 551, example 286 and pages 771-777, claim 52, definition of "G") demonstrating the interchangeability of the two groups at the E1 position.

Finding of prima facie obviousness-rationale and motivation (MPEP § 2142-2143)

One having ordinary skill in the art in possession of Barta et al. WO 00/69821 and Barta et al. WO 99/25687 would be in possession of such modification as a heteroaryl at the E1 position **because** such modification has been clearly guided to one skilled in the art in these references by exemplification of other analogous compounds. Both references teach structurally similar compounds which have utility as inhibitors of matrix metalloproteinase (see WO 00/69821, page 1, lines 13-24 and WO 99/25687, page 1, lines 7-17). Furthermore, Barta et al. demonstrated success in using the structurally similar compounds as MMP inhibitors in rats (see WO 99/25687, pages 731-734, especially example 379 and page 764, claim 28). One having ordinary skill in the art would be motivated to make such modification knowing that reasonable success has been demonstrated in analogous compounds. It is prima facie obvious to modify one known compound with attributes proven in analogous compounds.

10. Claims 1, 4-8, 10-55, 62, 69, 76 are rejected under 35 U.S.C. 103(a) as being obvious over Chen et al. (see WO 04/000811, pages 327-331, claim 1 and pages 434-435, claims 226, 228-229, 231) in view of Barta et al. WO 99/25687 (see WO 99/25687, pages 735-738, claim 1, page 764, claim 28 and pages 771-777, claim 52).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Determination of the scope and content of the prior art (MPEP§ 2141.01)

Chen et al. disclosed structurally similar compounds having utility as inhibitors of matrix metalloproteinase against the base claims as delineated (see WO 04/000811, page 1, lines 5-14, pages 327-331, claim 1 and pages 434-435, claims 226, 228-229, 231).

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The only difference between the instant claimed compound and the reference compound is that instead of E1 being aryl, E1 of the instant claimed compound is a heteroaryl group. Barta et al. however disclosed a structurally similar compound wherein E1 is optionally a heteroaryl or aryl group (see WO 99/25687, pages 771-777, claim 52, definition of "G") demonstrating the interchangeability of the two groups at the E1 position.

Finding of prima facie obviousness-rationale and motivation (MPEP § 2142-2143)

One having ordinary skill in the art in possession of Chen et al. WO 04/000811 and Barta et al. WO 99/25687 would be in possession of such modification as a heteroaryl at the E1 position **because** such modification has been clearly guided to one skilled in the art in these references by exemplification of other analogous compounds. Both references teach structurally similar compounds which have utility as inhibitors of matrix metalloproteinase (see WO 04/000811, page 1, lines 5-14 and WO 99/25687, page 1, lines 7-17). Furthermore, Barta et al. demonstrated success in using the structurally similar compounds as MMP inhibitors in rats (see WO 99/25687, pages 731-734, especially example 379 and page 764, claim 28). One having ordinary skill in the art would be motivated to make such modification knowing that reasonable success has been demonstrated in analogous compounds. It is prima facie obvious to modify one known compound with attributes proven in analogous compounds.

11. ***Double Patenting***

Claims 1, 4-8, 10-11, 13-14, 16-17, 20-36 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/270391 in view of claim 1 of US 6,890,937. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the copending claims when A2 and A3 together with the carbon to which they are bonded, form a heterocyclyl, and E2 is aryl. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims are narrower than the copending claims where E2 of the instant claims can only be carbocyclyl. The difference between the instant claimed compound and the copending compound is that instead of E1 being aryl, E1 of the instant claimed compound is heteroaryl. Claim 1 of US 6,890,937 however, teaches a structurally similar compound wherein E1 can be aryl or heteroaryl demonstrating the interchangeability of the two substituents at this position (see US 6,890,937, column 711, lines 61-62). One having ordinary skill in the art in possession of Application No. 11/270391 and US 6,890,937 would be in possession of such modification as E1 being heteroaryl **because** such modification has been clearly guided to one skilled in the art in these references by exemplification of other analogous compounds. Both references teach structurally similar compounds having utility for treating a mammal having a condition associated with pathological matrix metalloprotease activity (see 11/270391, Specification, page 1, lines 15-19 and US 6,890,937, column 718, claim 20). Furthermore, Barta et al. demonstrated success in using the structurally similar compounds to treat pathological conditions associated with matrix metalloprotease activity (see US 6,890,937, columns 701-711, Examples 444-448). One having ordinary skill in the art would be motivated to make such modification knowing that reasonable success has been demonstrated in analogous compounds. It is prima facie obvious to modify one known compound with attributes proven in analogous compounds.

12. Claims 1, 4-8, 10-11, 13-14, 16-17, 20-23, 26-36 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 67-70, 72-78, 103, 105-106, 112 of copending Application No. 10/747796 in view of claim 1 of US 6,890,937. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the copending claims when g=2, m=0, n=1 and p=1. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims are broader than the copending claims where E1 of the instant claims can be any heteroaryl and E2 can be any carbocyclyl. The difference between the instant claimed compound and the copending compound is that instead of E1 being a phenyl, E1 of the instant claimed compound is a heteroaryl and instead of E2 being a heterocycle, E2 of the instant claimed compound is carbocyclyl. Claim 1 of US 6,890,937 however, teaches a structurally similar compound wherein E1 can be aryl or heteroaryl demonstrating the interchangeability of the two substituents at this position (see US 6,890,937, column 711, lines 61-62) as well as a structurally similar compound wherein E2 can be a heterocycle or carbocyclyl demonstrating the interchangeability of the two substituents at the E2 position(see US 6,890,937, column 711, claim 1, lines 64-67). One having ordinary skill in the art in possession of Application No. 10/747796 and US 6,890,937 would be in possession of such modifications as E1 being heteroaryl and E2 being carbocyclyl **because** such modifications have been clearly guided to one skilled in the art in these references by exemplification of other analogous compounds. Both references teach structurally similar compounds having utility for treating a condition associated with pathological matrix metalloprotease activity (see 10/747796, Specification, page 1, lines 19-25 and US 6,890,937, column 718, claim 20). Furthermore, Barta et al. demonstrated success in using the structurally similar compounds to treat pathological conditions associated with matrix metalloprotease activity (see US 6,890,937, columns 701-711, Examples 444-448). One having ordinary skill in the art would be

motivated to make such modification knowing that reasonable success has been demonstrated in analogous compounds. It is prima facie obvious to modify one known compound with attributes proven in analogous compounds.

13. Claims 1, 4-8, 10-11, 13-14, 16-17, 20-36 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-12, 14-19 of U.S. Patent No. 6,541,489. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the patented claims when m=0, n=1, p=1, R14, Z is O and G is heteroaryl.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims are narrower than the patented claims where the Z-ring can only be a tetrahydropyran and G is only a heteroaryl. The difference between the instant claimed compound and the patented compound is that instead of G being heteroaryl or aryl, G of the instant claimed compound (E1) can only be heteroaryl. One having ordinary skill in the art in possession of US 6,541,489 would be in possession of the instant claims **because** the generic disclosure fully encompassed species of the instant claims (see US 6,541,489, column 723, claim 1). Furthermore, Barta et al. illustrated several structurally similar species rendering the instant claimed compound obvious in view of the generic teaching of aryl and heteroaryl substituents being interchangeable at the G position (see US 6,541,489, columns 601–654, Examples 213-388). Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention, to prepare any of the species of the genus taught by the reference, including those of the claims, because an ordinary artisan would have the reasonable expectation that all of the species of the

genus would have similar properties and, thus, the same use as the genus as a whole (see *In re* Lemin 141 USPQ 814).

14. Claims 1, 4-8, 10-11, 13-14, 16-17, 20-36 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 11-15, 17-23, 25, 27-30, 32-36 38-39 of U.S. Patent No. 6,890,937. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the patented claims when R3 is a heteroaryl, and Z is O.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The instant claims are narrower than the patented claims where the Z-ring can only be a tetrahydropyran and R3 is only heteroaryl. The difference between the instant claimed compound and the patented compound is that instead of R3 being heteroaryl or aryl, R3 of the instant claimed compound (E1) can only be heteroaryl. One having ordinary skill in the art in possession of US 6,890,937 would be in possession of the instant claims **because** the generic disclosure fully encompassed species of the instant claims (see US 6,890,937, column 711, claim 1). Furthermore, Barta et al. illustrated several structurally similar species rendering the instant claimed compound obvious in view of the generic teaching of aryl and heteroaryl substituents being interchangeable at the R3 position (see US 6,890,937, columns 590–643, Examples 213-388). Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention, to prepare any of the species of the genus taught by the reference, including those of the claims, because an ordinary artisan would have the reasonable expectation that all of the

species of the genus would have similar properties and, thus, the same use as the genus as a whole (see *In re* Lemin 141 USPQ 814).

15. ***Conclusion***

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Sarah E. Perlinger, whose telephone number is (571) 272-5574. The examiner can normally be reached on Monday through Friday, 8:30 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Thomas McKenzie, can be reached at (571) 272-0670. The fax number for the organization where this application or proceeding is assigned is (571)-273-8300.

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DP

06/01/2006

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